REMARKS

Claims 1-64 are pending, claims 14, 15, 17 and 18 having been amended and claims 29-64 having been added by the present amendment. The amendments and new claims are supported throughout the application as filed, e.g., at page 2, lines 1-8. Claims 1-13, 27 and 28 are withdrawn from consideration as being drawn to a non-elected invention. Upon entry of this amendment, claims 14-26 and 29-60 will be under examination.

Informalities

A sequence listing and response to the Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures is being submitted under separate cover directed to "Box Sequence" at the Arlington, VA address.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 14-26 are rejected "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." The Examiner states the following.

> The term "dedifferentiated pancreatic cells" in claim 1 is used by the claim to mean "a population of pancreatic cells or ductal cells substantially free from islet cells and obtained after islet isolation" while the accepted meaning is "dedifferentiation or re differentiation of pancreatic exocrine cells to a duct-like phenotype". (see reference by Kerr-Conte et al. [U] at page 1112, a the bottom of col. 2). Thus, it is uncertain as claimed what is a starting material in the claimed method. Is it a population of ductal cells? Or is it a treated (dedifferentiated) islet cell population?
>
> ↓ 1996 Diabetes.

This rejection is respectfully traversed. The meaning of the phrase "dedifferentiated pancreatic cells" would be clear to one of ordinary skill in the art when read in the context of the specification. Contrary to the Examiner's statement, the term "dedifferentiated pancreatic cells" is clearly used in the claims (and throughout the entire application as filed) to mean a population of adult or differentiated pancreatic cells that have been allowed to proliferate, thereby reverting

to a less differentiated state, i.e., a pluripotent state. This meaning is made clear by Applicants' specification, which provides as follows.

> [T]he invention features a method of promoting dedifferentiation of pancreatic cells. The method includes: obtaining a population of adult or differentiated pancreatic cells; and allowing the adult or differentiated cells to proliferate, e.g., rapidly proliferate, e.g., proliferate in the presence of an agent which promotes expansion, thereby providing dedifferentiated pancreatic cells. (See specification at page 2, lines 1-5)

The specification further explains that "[t]he dedifferentiated (pluripotent) cells can then be used to obtain islet cells, as well as duct cells and exocrine cells" (page 17, lines 13-15, emphasis added). See also page 32, line 6 et seq., of the specification, which further explains dedifferentiation as follows.

> Proliferation, e.g., rapid proliferation, of duct epithelial cells and/or exocrine cells can lead to the cells dedifferentiating back to a pluripotent state. Cells in this state are also referred to as dedifferentiated cells. Markers indicative of expansion can be used to detect cells in dedifferentiated state. Such markers can include cytokeratin, IPF-1 (PDX-1), Pref-1 and lack of insulin expression. (emphasis added).

In addition, the specification further appraises one of skill in the art as to the meaning and scope of the claims by providing detailed disclosure of how adult or differentiated pancreatic cells can be obtained (see, e.g., page 15, line 1 to page 16, line 6) and how their proliferation can be induced (see, e.g., page 16, line 8 to page 17, line 11) in order to make dedifferentiated pancreatic cells as defined in the specification. Accordingly, it would be clear to the ordinary artisan that dedifferentiated cells are adult or differentiated pancreatic cells that have been allowed to proliferate and thereby revert to a less differentiated state, i.e., a pluripotent state.

The Examiner cites Kerr-Conte et al. as providing that the accepted meaning of the phrase "dedifferentiated pancreatic cells" is "dedifferentiation or redifferentiation of pancreatic exocrine cells to a duct-like phenotype." However, Applicants do not agree that Kerr-Conte's use of the term "dedifferentiation" is "the accepted meaning." Even if it were, Applicants disagree with the Examiner's interpretation of Kerr-Conte's use of the term. In the passage quoted by the Examiner, Kerr-Conte states that "dedifferentiation (redifferentiation) of exocrine cells to a duct like phenotype has been documented in vitro in rodent and humans." Thus, Kerr-

Conte does nothing more than define "dedifferentiation" as the change from one pancreatic phenotype to another (in Kerr-Conte's case, from an exocrine phenotype to a duct phenotype). As discussed above, in Applicants' lexicography dedifferentiation is also the change from one pancreatic phenotype to another, specifically from an adult or differentiated pancreatic cell phenotype to a pluripotent phenotype brought on by proliferation of the differentiated cells. Thus, Applicants' definition is not inconsistent with Kerr-Conte's definition.

In another aspect of the rejection, the Examiner asserts that claim 1 is indefinite with regard to the phrase "component" because "it is not particularly clear whether it is a component of the extracellular matrix material or whether the extracellular matrix is a component of the whole culture system." Claim 1 has been amended to recite "adding a component of extracellular matrix," thereby obviating this rejection.

The Examiner also asserts that claim 15 is indefinite because "it is unclear whether the dedifferentiated cells were cultured till 70% confluence before or after adding matrix." This rejection has been met by amending claim 15 to recite that the cells are cultured until at least about 70% confluency before adding a component of extracellular matrix.

Claim 17 and 18 are said to be indefinite for containing "improper Markush groups." This rejection has been met by rewriting claims 17 and 18 as multiple claims (namely amended claims 17 and 18 and new claims 58-64), each reciting one member of the Markush group.

In a final aspect of this rejection, the Examiner asserts that claim 20 is indefinite because it is uncertain "whether a commercial Matrigel preparation is intended (see specification examples, for example page 40, line 6) or whether another preparation obtained from EHS tumor cells similar to Matrigel is intended." This aspect of the rejection is respectfully traversed. Applicants submit that claim 20 is quite clear on its face. A commercial Matrigel preparation is but one example of a preparation that one skilled in the art would understand to be "laid down by an Engelbreth-Holm-Swarm tumor cell," as recited in the claims. For example, one of skill in the art would recognize that a non-commercial basement membrane extract of Engelbreth-Holm-Swarm tumor cells can be made and used in the present claims.

In light of the foregoing, Applicants submit that the present claims are definite under 35 U.S.C. §112, second paragraph, and respectfully request that the Examiner's rejection be reversed.

Rejections Under 35 U.S.C. §102

All the claims are rejected as being anticipated by any of a number of cited references, which will be addressed in turn below. As discussed in detail below, each of the cited references discloses a method of obtaining pancreatic islet cells. However, none of the references discloses obtaining pancreatic islet cells from dedifferentiated pancreatic cells as recited in all of the presently pending claims.

Claims 14-26 are directed to a method of obtaining pancreatic islet cells from dedifferentiated pancreatic cells. The method includes adding a component of the extracellular matrix to a population of dedifferentiated pancreatic cells, and culturing the cells. Claim 29 and its dependent claims are directed to a method of obtaining pancreatic islet cells. The method includes: obtaining a population of dedifferentiated pancreatic cells made by (a) providing pancreatic duct or exocrine cells, and (b) allowing said duct or exocrine cells to proliferate to form a population of dedifferentiated pancreatic cells; adding a component of extracellular matrix to the population of dedifferentiated pancreatic cells; and growing the cells. Claim 41 and its dependent claims are directed to a method of obtaining pancreatic islet cells. The method includes: (a) obtaining a population of dedifferentiated pancreatic cells made by the process of (i) obtaining a population of adult or differentiated pancreatic cells substantially free of islet cells, and (ii) allowing the adult or differentiated pancreatic cells to proliferate; (b) adding a component of extracellular matrix to the population of dedifferentiated pancreatic cells; and (c) growing the cells.

As discussed above with regard to the § 112 rejection, dedifferentiated pancreatic cells are clearly defined in the specification as a population of adult or differentiated pancreatic cells that have been allowed to proliferate, thereby having reverted to a less differentiated state, i.e., a pluripotent state. The dedifferentiated (pluripotent) cells can then be redifferentiated into mature islet cells by adding a component of the extracellular matrix and growing them, as provided in the claims. Because none of the cited references use dedifferentiated cells as the starting

material for obtaining islet cells, none of the cited references anticipate the claims. Thus, this rejection is respectfully traversed in its entirety. Each of the cited references is addressed in turn below.

Kerr-Conte et al. 1996. Diabetes 45:1108-1114

Claims 14 and 16-26 are rejected as anticipated by Kerr-Conte. This rejection is traversed. Kerr-Conte describes the formation of ductal cysts starting with purified islet preparations obtained by "hand picking of islets to reduce contaminating exocrine tissue and ductal fragments" (see, e.g., page 1109, top of first column and first paragraph of results). The purified islets are cultured in rat-tail collagen or Matrigel and evaluated for ductal cyst formation. Kerrr-Conte provides as follows.

> This study demonstrates that under appropriate culture conditions (RT collagen gels or Matrigel), adult human islet preparations resulted in an expansion of the ductal epithelial components.

Kerr-Conte does not mention or suggest that the purified islets are dedifferentiated (i.e., islets that have been allowed to proliferate to revert to a pluripotent state), as required by claims 14-26. Much less does Kerr-Conte disclose the use of dedifferentiated cells derived from a population of duct or exocrine cells or a population substantially free of islet cells, as required by claims 29-64. To the contrary, Kerr-Conte uses highly purified adult islet cells as a starting material. Therefore, Kerr-Conte does not anticipate the present claims.

Rawdon et al. 1998. Microscopy Research and Technique 43:292-305

Claims 14 and 16-26 are rejected as anticipated by Rawdon. This rejection is traversed. Rawdon discloses a method of producing insulin cells by culturing dorsal pancreatic buds of chick embryos on collagen gel or matrigel (see, e.g., abstract and Figure 4). Clearly, because these pancreatic bud cells are embryonic, they are undifferentiated to begin with. Nowhere does Rawdon disclose starting with adult or differentiated cells, much less dedifferentiated adult cells, as required by all the claims. Therefore, Rawdon does not anticipate the claims.

Archer et al. U.S. Patent No. 4,439,521

Claims 14-17 and 22-26 are rejected as anticipated by Archer. The Examiner states:

> US 4,439,521 discloses a method of obtaining or regenerating pancreatic islets wherein the method comprises steps of adding an extracellular matrix (plastic dish) to a population of dedifferentiated pancreatic cells or ductal tissue free from islets (col. 9, line 16), culturing the cells till 70% of confluency or attachment of ductal cells (col. 9, line 23) are and obtaining/regenerating pancreatic islet cells (col. 9, lines 45-68).

This rejection is traversed. Archer discloses obtaining islet like structures by culturing primary duct cells, pancreatic islets, pancreatic duct pieces, or pancreatic cell clusters directly on a plastic substrate. See, e.g., the Archer abstract and the discussion on column 1, lines 50-56, as follows.

> In the method of the invention, one or more usually a plurality of pancreatic tissue-derived bodies are cultured in a liquid culture medium under conditions promoting mammalian cell growth with the said bodies being attached to a compatible substrate for a period sufficient to result in the neogenesis of ILS's connected to the substrate adjacent the said body or bodies.

Thus, Archer does not disclose culturing dedifferentiated cells as defined in Applicants' specification. Nor does Archer teach or suggest adding a component of the extracellular matrix to the cells, as required by all the claims. Contrary to the Examiner's argument, a plastic dish is not an extracellular matrix or a component of the extracellular matrix. A plastic dish is merely a substrate for attachment of the cells. One of skill in the art would understand that a component of the extracellular matrix, as recited in the claims, means a biological component. Therefore, Archer does not anticipate the present claims.

Dudek, U.S. Patent No. 4,935,000

Claims 14, 16-19 and 21-26 are rejected as anticipated by Dudek. This rejection is respectfully traversed. Dudek describes the production of pancreatic islet tissue by adding fetal mesenchyme to adult ductal epithelium. See Figure 1 of Dudek, which outlines the disclosed procedure. See also column 4, lines 21-36, which provides as follows.

> A specific embodiment of the present invention involves the interaction of an extracellular matrix, such as fetal mesenchyme with a pancreatic ductal epithelium to produce pancreatic islet tissue. It is applicable, however, to any

> tissue having a ductal element and contemplates using a patient's own tissue as a source of transplantable differentiated tissue. The extracellular matrix or mesenchymal can be obtained from a fetal source, a lower phylogenetic source, or from chemically defined material, isolated from biological sources, chemically synthesized or genetically engineered.
> More specifically, in a method of producing pancreatic islet tissue, the method of the invention involves the recombination of substantially pure adult ductal epithelium with fetal duodenal mesenchyme as the extracellular matrix (emphasis added).

Thus, Dudek does not disclose--or even contemplate--adding fetal mesenchyme to dedifferentiated cells. Rather, Dudek only discloses adding mesenchyme to adult or differentiated ductal epithelial tissue. Therefore, Dudek does not anticipate the claims.

In light of the foregoing, Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. §103

Claims 14-26 are rejected as being unpatentable over Kerr-Conte, Rawdon, Archer and Dudek taken with U.S. Patent No. 5,681,587, U.S. Patent No. 4,829,000 and Bonner-Weir et al. 1994 TEM 5:60-64. The Examiner argues as follows.

> It would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the methods of the cited references with a reasonable expectation of success in producing hormone positive or insulin producing islet cells because the idea of islets regeneration or neogenesis of islets from ductal cells or dedifferentiated pancreatic cells has been known in the prior art as demonstrated by the cited references. The use of particular matrix for cell attachment of development is considered to be within the knowledge available to regular practitioner particularly in view that Matrigel (EHGS preparation) is known and suggested as superior material for producing islets. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in absence of evidence to the contrary.

This rejection is respectfully traversed. To establish prima facie obviousness of a claimed invention, "the prior art reference (or references when combined) must teach or suggest all the claim limitations" (see MPEP § 706.02(j), emphasis added). In addition, the prior art must provide a motivation and a reasonable expectation of success to combine the references to arrive at the invention. In this instance, a prima facie case of obviousness has not been made because the cited references, alone or in any combination, do not teach or suggest all the claim

limitations. As discussed in detail below with regard to the §102 rejection, each of Kerr-Conte, Rawdon, Archer and Dudek disclose a different type of cell or tissue as a staring material for a method of obtaining islet cells. However, none of the references discloses or suggests the use of dedifferentiated pancreatic cells, as recited in all the claims. Neither U.S. 5,681,587, U.S. 4,829,000 nor Bonner-Weir et al., either alone or in any combination, make up for the deficiencies of the primary references. Therefore, the present claims are patentable over the cited references.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a check for excess claim fees and a Petition for Extension of Time with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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Version with markings to show changes made

In the claims:

Claims 14, 15, 17 and 18 have been amended as follows:

14. (Amended) A method of obtaining pancreatic islet cells from dedifferentiated pancreatic cells, comprising:

adding a component of [an] extracellular matrix [component] to a population of dedifferentiated pancreatic cells; and

culturing the cells, [to] thereby obtaining pancreatic islet cells.

15. (Amended) The method of claim 14, wherein the population of dedifferentiated pancreatic cells has been cultured until at least about 70% confluency before adding the component of extracellular matrix.

17. (Amended) The method of claim 16, wherein the marker is [one or more of:] cytokeratin[, IPF-1, Pref-1, and lack of insulin].

18. (Amended) The method of claim 14, wherein the component of extracellular matrix [component] is [selected from the group consisting of:] laminin[, collagen, entactin, heparin sulfate proteoglycan, and nidogen].